PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2005/000902	18.08.2005	19.08.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/403 A61K31/404 A61K31/415 A61K31/4164 C07D209/32 C07D209/12 A61P25/28 A61P5/50

Applicant
TEL AVIV UNIVERSITY FUTURE TECHNOLOGY ...

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	see form PCT/ISA/210	Cielen, E Telephone No. +31 70 340-4540

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2005/000902

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2005/000902

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-84 (all partially); 1-19 (with respect to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 1-19 (with respect to industrial applicability) relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1-84 (all partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	11-19, 30-38, 49-50, 57, 68-69, 76
	No:	Claims	1-10, 20-29, 39-48, 51-56, 58-67, 70-75, 77-84
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-84
Industrial applicability (IA)	Yes:	Claims	20-84
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.i. Present claims 1-19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

III.ii. Present claims 1-76 refer to the treatment of diseases which actually are not well defined. The use of the definition "an amyloid associated disease" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT.

It is not fully possible to determine the diseases for which protection might legitimately be sought. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the real and defined diseases mentioned in the description, p. 22, lines 6-20, with due regard to the general idea underlying the application.

III.iii.(a) Present claims 1-9, 13, 14, 16, 17, 19-28, 32, 33, 35, 36, 38-47, 51, 52, 54, 55, 57-66, 70, 71, 73, 74 and 76-84 relate to an extremely large number of possible compounds, namely the Markush formula with numerous options and also the term "or a prodrug thereof". Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds claimed. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of the above-mentioned claims (PCT Guidelines 9.19 and 9.23). The search of these claims was restricted to those claimed compounds which appear to be supported and disclosed, namely the indole compounds mentioned in claims 10-12, 15, 18, 29-31, 34, 37, 48-50, 53, 56, 67-69, 72 and 75 and the compounds mentioned in the description, p. 31, lines 5-12 and the examples, with due regard to the general idea underlying the application.

(b) Moreover, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty for claims 77-84. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search of these claims. The search of claims 77-84 was restricted to the indole compounds

having a hydroxy, halo or hydroxymethyl group directly attached to the indole ring in any of the positions R_1-R_{10}, where all other substituents are hydrogen, with due regard to the general idea underlying the application.

III.iv. No opinion will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT) (see also item **V.i**).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.i.(a) Attention is drawn to the fact that the present statement expressed as to novelty, inventive step and industrial applicability refers only to matter for which an International Search Report has been drawn up (i.e. only for pharmaceutical compositions and articles-of-manufacture containing the indole compounds mentioned in claims 10-12, 15, 18, 29-31, 34, 37, 48-50, 53, 56, 67-69, 72 and 75, the compounds mentioned in the description, p. 31, lines 5-12 and the examples, and their use for the treatment of the diseases mentioned in the description, p. 22, lines 6-20, and for indoles having a hydroxy, halo or hydroxymethyl group directly attached to the indole ring in any of the positions R_1-R_{10}, where all other substituents are hydrogen, with due regard to the general idea underlying the application).

(b) Present claims 1-19 involve compositions or substances in a method of treatment of the human/animal body. For the assessment of such claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.ii. Reference is made to the following documents:

D1 : US 2001/041732 A1 (GURLEY DAVID ET AL) 15 November 2001 (2001-11-15)

D2 : NAKAJIMA, TERUO: "Amine precursor therapy: manipulation of brain amine activity with precursor amino acid" PSYCHIATRY AND CLINICAL NEUROSCIENCES , 51(5), 267-274 CODEN: PCNEFP; ISSN: 1323-1316, 1997, XP008064215

D3 : WO 03/039540 A (SEPRACOR INC; HEEFNER, DONALD, L; CURRIE, MARK, G; ROSSI, JR., RICHARD) 15 May 2003 (2003-05-15)

D4 : WO 03/070269 A (SCHRAERMEYER, ULRICH) 28 August 2003 (2003-08-28)

D5 : EP 0 421 946 A (POLIFARMA S.P.A) 10 April 1991 (1991-04-10)

D6 : WO 99/42102 A (SOUTH ALABAMA MEDICAL SCIENCE FOUNDATION; NEW YORK UNIVERSITY) 26 August 1999 (1999-08-26)

D7 : US 2004/029830 A1 (HEBERT ROLLAND F) 12 February 2004 (2004-02-12)

D8 : LEE, MIN WON ET AL: "Anti- diabetic constituent from the node of lotus rhizome (Nelumbo nucifera Gaertn)" NATURAL PRODUCT SCIENCES , 7(4), 107-109 CODEN: NPSCFB; ISSN: 1226-3907, 2001, XP001154675

D9 : WO 03/024443 A (UNIVERSITY OF FLORIDA; MARTYNYUK, ANATOLY, E; DENNIS, DONN, MICHAEL; G) 27 March 2003 (2003-03-27)

D10 : WO 00/24390 A (THE UNIVERSITY OF BRITISH COLUMBIA; REINER, PETER, B; LAM, FRED, CHIU-) 4 May 2000 (2000-05-04)

D11 : DATABASE WPI 2 June 2000 (2000-06-02), Derwent Publications Ltd., London, GB; Class 021,page 9, AN 2000-451668 XP002382814 HONMA T. ET AL.: "Use of a thromboxane A2 antagonist or synthase inhibitor for treating central nervous system diseases, e..g. Alzheimer type dementia." &; WO 00/30683 A (SHIONOGI &; CO LTD) 2 June 2000 (2000-06-02)

D12 : US 2004/152672 A1 (CARSON DENNIS A ET AL) 5 August 2004 (2004-08-05)

D13 : LOSERT W ET AL: "Effects of indole 3 alkanecarboxylic acids on glucose utilization in rats" ARZNEIMITTEL-FORSCHUNG/DRUG RESEARCH 1975, vol. 25, no. 6, 1975, pages 880-887, XP008064216

D14 : DATABASE WPI 20 January 2003 (2003-01-20), Derwent Publications Ltd., London, GB; Class 032,page 8, AN 2003-286683 XP002382815 KISELEV V.I. ET AL.: "Pharmaceutical composition for prophylaxis and treatment of uterus cervix dysplasia and cancer and larynx papillomatosis and methods of prophylaxis and treatment of said sicknesses

based on thereof." &; RU 2 196 568 A (KISELEV VSEVOLOD IVANOVICH) 20 January 2003 (2003-01-20)

D15 : KAZUMI KON-YA ET AL: "INDOLE DERIVATIVES AS POTENT INHIBITORS OF LARVAL SETTLEMENT BY THE BARNACLE, BALANUS AMPHITRITE" BIOSCIENCE BIOTECHNOLOGY BIOCHEMISTRY, JAPAN SOC. FOR BIOSCIENCE, BIOTECHNOLOGY AND AGROCHEM, TOKYO, JP, vol. 58, no. 12, 1994, pages 2178-2181, XP008064229 ISSN: 0916-8451

D16 : P. APPUKKUTTAN, E. VAN DER EYCKEN, W. DEHAEN: "Microwave enhanced formation of electron rich arylboronates" SYNLETT, no. 8, 2003, pages 1204-1206, XP002382809

D17 : US 3 042 685 A (ROUSSEL UCLAF) 3 July 1962 (1962-07-03)

D18 : DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002382811 Database accession no. 116671 (BRN)

D19 : US 2 920 080 A (LES LABORATOIRES FRANÇAIS DE CHIMIOTHERAPIE) 5 January 1960 (1960-01-05)

D20 : US 3 625 973 A (MARC JULIA) 7 December 1971 (1971-12-07)

D21 : FR 1 373 316 A (SANDOZ S. A) 25 September 1964 (1964-09-25)

D22 : US 3 790 596 A (SHKILKOVA V,SU ET AL) 5 February 1974 (1974-02-05)

D23 : US 3 976 639 A (BATCHO ET AL) 24 August 1976 (1976-08-24)

D24: COHEN T. ET AL.: "Inhibtion of amyloid fibril formation and cytotoxicity by hydroxyindole derivatives" BIOCHEMISTRY, vol. 45, 2006, pages 4727-4735, XP002382810

V.iii. Article 33(2) PCT.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-10, 20-29, 39-48, 51-56, 58-67, 70-75 and 77-84 is not new in the sense of Article 33(2) PCT.

(a) Attention is drawn to the fact that the scope of claims 39-76 for which protection is sought as it is worded is regarded as a so-called "first medical use". Claims drafted in this way are only allowable if no other medical use has been earlier disclosed. Consequently, any

document disclosing a medical use of a composition comprising a compound of formula I will be novelty-destroying for the subject-matter of those claims.

A claim for a package or a kit comprising a product together with instructions for its use in a medical treatment amounts to a claim for a first medical use. Such a claim is not novel if it is not the first time that the product has been used in a medical treatment.

Even if it were considered that the kit is novel over the prior art product, because the instructions on the notice are different, the only difference between the invention and the prior art, and therefore the invention itself, would reside in a pure presentation of information. Such an invention is excluded from patentability under Rule 67.1(v) PCT.

(b) Present claims 1-76 relate to the mechanism underlying the treatment of the claimed diseases with the compounds of the present invention. However, the mere explanation of an effect obtained when using a compound in a known composition, even if the effect was not known to be due to this compound in the known composition, cannot confer novelty on a known process if the skilled person was already aware of the occurrence of the desired effect. Even if the inhibition of amyloid fibril formation by the compounds of the present invention is indisputably a pharmacological effect, it cannot in itself be considered a therapeutic application, nor can it render the known treatment of a specified pathological condition, in the present case the known treatment of the diseases mentioned in the description, p. 22, lines 6-20, novel. Although the discovery of such a mechanism may be an important piece of scientific knowledge, it cannot be considered as a technical contribution to the art, since it still needs to be turned into a practical application in the form of a specified actual treatment of the pathological condition. In the present case, the specified actual treatment of the diseases mentioned in the description, p. 22, lines 6-20 was already disclosed in the cited prior art documents (see below).

Consequently, whatever the merit of the scientific teaching provided by the application regarding the mechanism of action of the claimed compounds, it is only the therapeutic effect of the medicament, i.e. treating the diseases mentioned in the description, p. 22, lines 6-20, which is relevant for the assessment of novelty and inventive step within the meaning of Articles 33(2) and 33(3) PCT.

(c) Document D1 discloses the use of a modulator of a nicotine receptor agonist, which preferably is 5-hydroxyindole, for the treatment of e.g. Alzheimer's, Parkinson or Huntington's disease (par. [0021], [0029], [0039]; claims 5, 7, 9, 10). Therefore, the subject-matter of present claims 1-4, 6-8, 20-23, 25-27, 39-42, 44-46, 58-61 and 63-65 is not novel over D1.

(d) Document D2 teaches the use of L-5-hydroxytryptophan for the treatment of

Parkinson's disease (p. 269, left-hand column, par. 2-3). Therefore, the subject-matter of present claims 1-4, 6-8, 20-23, 25-27, 39-42, 44-46, 58-61 and 63-65 is not novel over D2.

(e) Document D3 reports the use of, inter alia, 5-hydroxy-2-indole carboxylic acid for the treatment of Parkinson's, Huntington's or Alzheimer's disease (par. [0002], [0016]-[0017], [0041], [0043]-[0044], [0047]; claims 1, 4, 7, 8, 11). Therefore, the subject-matter of present claims 1-4, 6-8, 20-23, 25-27, 39-42, 44-46, 58-61, 63-65, 77-80, 82 and 83 is not novel over D3.

(f) Document D4 describes the use of 5,6-dihydroxyindole or 5,6-dihydroxyindole-2-carboxylic acid for the treatment of, inter alia, Parkinson's disease (p. 1, par. 1; p. 3, par. 5; p. 6, par. 3; claim 2). Therefore, the subject-matter of present claims 1-4, 6-8, 20-23, 25-27, 39-42, 44-46, 58-61, 63-65, 77-80, 82 and 83 is not novel over D4.

(g) Document D5 teaches the use of 4-hydroxy-indol-3-yl-pyruvic acid and related compounds for the treatment of, inter alia, Alzheimer's disease (p. 2, lines 1-15, 44-46; examples 4, 5; p. 8, lines 39-40; claims 6-8). Therefore, the subject-matter of present claims 1-10, 20-29, 39-48, 58-67 and 77-83 is not novel over D5.

(h) Document D6 discloses the use of indole-3-propionic acid to prevent the cytotoxic effects of amyloid beta protein. It can be used for the treatment of Alzheimer's, Parkinson's and prion-related diseases (p. 4, lines 8-18; p. 5, lines 18-21; p. 5, line 31 - p. 6, line 8; p. 6, line 24 - p. 7, line 12; p. 10, line 24 - p. 11, line 27; examples 1, 6; claims 1, 9, 11, 12, 19-24). Therefore, the subject-matter of present claims 1-5, 20-24, 39-43 and 58-62 is not novel over D6.

(i) Document D7 discloses that salts of indole-3-propionic acid with chitosan can be used for the treatment of diseases involving free radicals or oxidative stress, such as Parkinson's or Alzheimer's disease or diabetes, or for the treatment of fibrillogenic diseases to prevent the cytotoxicity of amyloid beta protein, such as prion related diseases, Parkinson's disease or amyloidosis (par. [0003], [0012]-[0013], [0015], [0023]-[0025]; claims 1, 4-7, 10, 12, 13). Therefore, the subject-matter of present claims 1-5, 20-24, 39-43 and 58-62 is not novel over D7.

(j) Document D8 reports that tryptophan and tryptamine have potential antidiabetic activity (abstract; p. 108, left-hand column, last par. - right-hand column, par. 1). Therefore, the subject-matter of present claims 1-5, 20-24, 39-43 and 58-62 is not novel over D8.

(k) Document D9 discloses the treatment of a neurological condition characterised by excessive activity of glutamatergic ionotropic receptors, e.g. Alzheimer's or Huntington's disease, with aromatic amino acids, such as L- or D-tryptophan (par. [0010], [0012], [0014],

[0073]; claims 1-3, 14, 16, 48, 51, 53, 66, 69). Therefore, the subject-matter of present claims 1-5, 20-24, 39-43 and 58-62 is not novel over D9.

(l) Document D10 reports that compounds which modulate the production and/or release of amyloid beta protein and amyloid deposition, which can be tryptamine, can be used for the treatment of Alzheimer's disease, amyloidosis, prion-related diseases or adult onset diabetes (p. 8, line 29 - p. 9, line 6; p. 21, lines 13-17; p. 23, lines 1-7; p. 24, line 16 - p. 25, line 2; claims 1, 2, 11, 12, 15-17, 20, 21, 24, 29, 30, 53, 54, 63, 64, 67, 68). Therefore, the subject-matter of present claims 1-5, 20-24, 39-43 and 58-62 is not novel over D10.

(m) Document D11 discloses the use of a compound (L-655,240; claim 12) which fits in present formula (I) for the treatment of CNS diseases of the Alzheimer type. The compound inhibits nerve cell denaturation caused by amyloid beta protein. Therefore, the subject-matter of present claims 1-4, 6, 20-23, 25, 39-42, 44, 58-61, 63, 77-80 and 82 is not novel over D11.

(n) Document D12 describes fused tricyclic compounds, which fit in formula I, for the treatment of cancer, such as multiple myeloma (par. [0010]-[0011], [0014], [0070]; claims 1, 3 and 9). Therefore, the subject-matter of present claims 1-3, 20-22, 39-41, 58-60 and 77-79 is not novel over D12.

(o) Document D14 discloses the first medical use of indole-3-carbinol. In view of item **V.iii(a)**, the subject-matter of present claims 39-46, 51-56, 58-65 and 70-75 is not novel over D14.

(p) Document D15 discloses indole-3-ethanol (compound 102) and several other compounds which fit in formula I per se (e.g. compounds 14, 31-34). Therefore, the subject-matter of present claims 77-84 is not novel over D15.

(q) Document D16 discloses 4- or 5- or 6- or 7-bromo-indole (Scheme 4; compounds 5a-5d). Therefore, the subject-matter of present claims 77-83 is not novel over D16.

(r) Document D17 discloses 6-fluoroindole and other compounds which fit in general formula I (examples 3, 4, 6, 7). Therefore, the subject-matter of present claims 77-80 and 82 is not novel over D17.

(s) Document D18 discloses indol-2-yl-methanol. Therefore, the subject-matter of present claims 77-80 and 82-84 is not novel over D18.

(t) Document D19 discloses 5- or 6- or 7-chloroindole, 5,6-dimethoxyindole, 6-methylindole, 5- or 6-methoxyindole per se (column 2, lines 31-45). Therefore, the subject-matter of present claims 77-80 and 82 is not novel over D19.

(u) Document D20 discloses 4- or 7-hydroxyindole, 4-ethoxyindole per se (column 1, lines 4-8; examples 4-6). Therefore, the subject-matter of present claims 77-80, 82 and 83 is

not novel over D20.

(v) Document D21 discloses 4- or 5- or 6- or 7-hydroxymethylindole per se (p. 2, column 2, line 40; p. 3, column 1, lines 18, 55, 56; p. 3, column 2, lines 28, 29). Therefore, the subject-matter of present claims 77-84 is not novel over D21.

(w) Document D22 discloses 5-chloro, 5-bromo, 5-methyl-, 2-methyl-, 3-ethyl- or 5-methoxy-2-methylindole per se (examples 3-5, 7-9). Therefore, the subject-matter of present claims 77-80 and 82 is not novel over D22.

(x) Document D23 discloses 6-chloro-, 5-chloro-, 5-fluoro-, 4-chloro-, 6-cyano- or 5,6-dimethyl-indole per se and other compounds which fit in formula I (examples 20, 22, 24, 26, 29, 35, 37, 44, 47, 51, 53, 55). Therefore, the subject-matter of present claims 77-80 and 82 is not novel over D23.

V.iv. Article 33(3) PCT.

(a) The problem to be solved by the present application is the provision of an alternative medicine for the treatment of amyloid associated diseases. The proposed solution is the use of indole derivatives.

(b) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-84 - as far as novel - does not involve an inventive step in the sense of Article 33(3) PCT.

Even if novelty could be restored, the present application would very likely lack an inventive step over each of D1-D12, which clearly teach the use of the presently claimed compounds for the treatment of the claimed amyloid associated diseases.

(c) Moreover, it appears that the problem underlying the present application has not been solved by all of the claimed variants for the following reasons:

1. Document D13 discloses that there is no justification for the use of alkane-3-carboxylic acids for the treatment of diabetes mellitus (p. 880, left-hand column, par. 6; p. 886, right-hand column, par. 4-5; p. 887, left-hand column, par. 3).

2. The experimental results in the present description provide positive data only for 3-hydroxyindole, 4-hydroxyindole and indole-3-carbinol. On p. 32, line 30 - p. 33, line 10, it is stated that "indole derivatives having a carboxylic acid or an alkyl attached directly or indirectly to the indole ring did not exhibit an effective inhibition of amyloid formation".

3. Equally, the post-published document D24 by the present authors teaches that

unmodified indole, 3-methylindole, indole-3-ethanol, indole-3-propionic acid and 5-hydroxyindole did not significantly inhibit the aggregation of amyloid beta peptide (abstract; ; p. 4728, left-hand column, last par. - right-hand column, par. 2; p. 4729, left-hand column, par. 4). It is concluded that a hydroxyl group positioned on C3 or C4 of the indole ring is required to potently inhibit beta amyloid formation (p. 4732, right-hand column, par. 2). The position of the hydroxyl group therein is of key importance (p. 4732, right-hand column, par. 2-3; p. 4733, right-hand column, par. 4).

The presence of an inventive step cannot be recognised for problems which have not been solved or which have not been solved by all variants.

Re Item VII
Certain defects in the international application

There is an inconsistency in the claim dependency of claims 80-82. They refer to an article-of-manufacture, whereas they depend on claim 77, which is a compound claim.

Re Item VIII
Certain observations on the international application

VIII.i.(a) Present claims 1-9, 13, 14, 16, 17, 19-28, 32, 33, 35, 36, 38-47, 51, 52, 54, 55, 57-66, 70, 71, 73, 74 and 76-84 relate to an extremely large number of possible compounds, which are all supposed to be effective in the treatment of amyloid associated diseases. In fact, the number of claimed variants cannot be estimated without undue burden and in any case appears to be fully disproportionate to what actually is disclosed and supported by pharmacological evidence.

As a rule, protection conferred by a patent should be commensurate with the range of compounds for which the effect has been properly demonstrated, including obvious variants thereof. In this respect, the number of claimed variants has to be justified by the extent of the description and drawings and also the contribution to the art in consideration of the nature of the invention claimed.

Having to construe the numerous variants comprised in claims 1-9, 13, 14, 16, 17, 19-28, 32, 33, 35, 36, 38-47, 51, 52, 54, 55, 57-66, 70, 71, 73, 74 and 76-84 and to form an opinion on whether or not any one of them could be effective in the treatment of amyloid associated diseases imposes a severe and totally undue burden on the skilled person.

(b) Moreover, present claims 77-84 relate to an extremely large number of compounds *per se* for which no reaction schemes and/or synthetic data are provided. Given the very diverse nature of the substituents, the skilled person would not know how to synthesise these compounds.

(c) It follows that the present application as it stands falls foul of the clear provisions of Articles 5 and 6 PCT.